

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of )  
Einar STEFANSSON ) Group Art Unit: 1614  
Application No.: 09/925,659 ) Examiner: Zohreh A. Fay  
Filed: August 10, 2001 ) Confirmation No.: 4462  
For: METHOD FOR THE PREVENTION )  
AND TREATMENT OF RETINOPATHY )

**RECEIVED**

**MAR 09 2004**

**THIRD INFORMATION DISCLOSURE STATEMENT**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

In accord with the requirements set forth in 37 C.F.R. §§ 1.56, 1.97 and 1.98, applicant is submitting herewith a Form PTO-1449 listing documents for consideration by the Examiner.

Copies of all of the documents listed on the Form PTO-1449 are enclosed.

These documents are being submitted after a first Office Action on the merits but prior to the closing of prosecution, therefore under 37 C.F.R. § 1.97(c), the fee set forth in 37 C.F.R. § 1.17(p) is enclosed.

The first fourteen literature references listed on the accompanying Form PTO-1449 are numbered [1] through [14]. These fourteen documents are being cited to support the position taken by applicant in the accompanying amendment are referred to by the same numbers therein, where they are discussed.

The remaining documents listed on the accompanying Form PTO-1449 are discussed below.

Stefansson et al. U.S. Patent No. 6,156,785 and its PCT counterpart, WO 99/37292, concern an earlier invention by applicant and his coinventors which relate to treatment of glaucoma with carbonic anhydrase inhibitors, based on the discovery that the carbonic anhydrase inhibitors increased oxygen tension in the optic nerve and retina. Prior methods

for the treatment of glaucoma focused on the elevated intraocular pressure associated with the disease.

Prior to the present invention, prevention and treatment of retinopathies took a number of different forms. The enclosed copy of a medical progress report/review article by Robert N. Frank, M.D. on diabetic retinopathy, a copy of which appeared in the January 1, 2004 issue of the New England Journal of Medicine, gives a very good indication of what the methods are at this time; see, for example, Table 1 on page 50. This article also indicates the proposed pathogenic mechanisms for diabetic retinopathy; see, for example, Table 2 on page 51, which in fact only lists oxygen as a harmful substance. It can be seen from these tables in particular that the hypothesis that oxygen may play a positive role in the treatment of diabetic retinopathy is not generally accepted. Indeed, it has not been taken seriously by researchers in the field, who are now primarily focusing on growth factors and transmitters.

Further support for the present inventor's position that the art did not accept a hypothesis that oxygen may play a role in treating diabetic retinopathy is provided by three additional review articles submitted herewith.

The first of these is a major review on diabetic retinopathy by Lloyd M. Aiello, MD, a respected authority in the field, which was published in the American Journal of Ophthalmology in July of 2003. Hypoxia is mentioned once related to a 1948 reference; this has been underlined for the Examiner's convenience. Clearly, mainstream authorities do not believe oxygen plays a role in diabetic retinopathy. (Please note that the figures and tables for this article appear after the bibliography at the end of the article because they had to be down-loaded separately.)

The second of these is another major review, which appeared in Survey of Ophthalmology, a highly respected journal, in December of 2002, is by Donald S. Fong MD, MPH. The only mention of oxygen, which is underlined for the Examiner's convenience, refers to the damaging potential of an oxygen reactive species. Here oxygen is seen as harmful and is never mentioned as being possibly helpful.

The third additional review article, by Fong et al., appearing in Diabetes Care in 2003, again ignores any helpful role of oxygen in the treatment of diabetic retinopathy.

Thus, it is clear from these three articles together with the Frank review article that leaders in the field of retinopathy do not subscribe to the oxygen theory upon which the present inventor has based the present invention. Despite this teaching away by others in the field, as evidenced by these review articles, the present inventor came to believe that increasing oxygen tension in the optic nerve and retina pharmacologically could treat retinopathies including diabetic retinopathy. He then turned to the carbonic anhydrase inhibitors, which he had previously worked with in treating glaucoma successfully based on increasing oxygen tension in the optic nerve and retina, and found that his hypothesis did in fact work in retinopathy (as shown in the instant specification).

It was not obvious to turn to the carbonic anhydrase inhibitors because they are glaucoma drugs and it is not obvious that a glaucoma drug would be useful for treating diabetic or other retinopathies. These are generally considered to be completely different diseases, handled by different subspecialties within ophthalmology, and they have a different pathophysiology. And as a mechanism regarding oxygen tension was not an accepted hypothesis for retinopathy, it would not occur to the ordinary skilled worker to use the carbonic anhydrase inhibitors to increase oxygen tension in the optic nerve and retina and to thus treat retinopathy.

As the Examiner is aware, there were researchers who earlier treated macular edema with carbonic anhydrase inhibitors (references already of record). As noted in the accompanying response, macular edema occurs in some but not the vast majority of patients having diabetic retinopathy and does not occur at all in certain other kinds of retinopathies. Moreover, the researchers who hold the earlier macular edema patents based their scientific rationale on the effect carbonic anhydrase inhibitors have on the pumping of the retinal pigment epithelium. Exactly because of this different scientific rationale, it would not have been obvious that carbonic anhydrase inhibitors would help any other part of diabetic retinopathy than the macular edema. The pumping of the retinal pigment epithelium might help dry the macular edema of the excessive water but would not have any effect on any other aspects of diabetic retinopathy. It is only through the present inventor's rationale that the conclusion can be reached that one can use a carbonic anhydrase inhibitor to treat a patient who has retinopathy but does not have macular edema.

**THIRD** Information Disclosure Statement

Application No. 09/925,659

Attorney's Docket No. 032904-001

Page 4

For the reasons set forth above as well as those set forth in the accompanying Reply and Amendment, it is submitted that the present invention is free of the record rejection and of any potential rejections based on the art cited herein.

It is respectfully requested that an Examiner-initialed copy of the accompanying Form PTO-1449 be returned to the undersigned with the next official communication.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date February 27, 2004

By: Mary Katherine Baumeister  
Mary Katherine Baumeister  
Registration No. 26,254

P.O. Box 1404  
Alexandria, Virginia 22313-1404  
(703) 836-6620



Patent  
Attorney Docket No. 032904-001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Einar STEFANSSON

Application No.: 09/925,659

Filing Date: August 10, 2001

Title: METHOD FOR THE PREVENTION AND  
TREATMENT OF RETINOPATHY

Group Art Unit: 1614

Examiner: Zohreh A. Fay

Confirmation No.: 4462

RECEIVED

MAR 09 2004

THIRD  
INFORMATION DISCLOSURE STATEMENT  
TRANSMITTAL LETTER

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Enclosed is a THIRD Information Disclosure Statement and accompanying form PTO-1449 for the above-identified patent application.

- ☐ No additional fee for submission of an IDS is required.
- ☒ The fee of \$180.00 (1806) as set forth in 37 C.F.R. § 1.17(p) is also enclosed.
- ☐ A statement under 37 C.F.R. § 1.97(e) is also enclosed.
- ☐ A statement under 37 C.F.R. § 1.97(e), and the fee of \$180.00 (1806) as set forth in 37 C.F.R. § 1.17(p) are also enclosed.
- ☐ Charge \_\_\_\_\_ to Deposit Account No. 02-4800 for the fee due.
- ☐ A check in the amount of \_\_\_\_\_ is enclosed for the fee due.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800. This paper is submitted in duplicate.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

P.O. Box 1404  
Alexandria, Virginia 22313-1404  
(703) 836-6620

Date: February 27, 2004

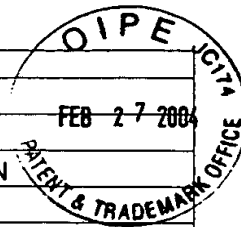
By Mary Katherine Baumeister  
Mary Katherine Baumeister  
Registration No. 26,254

03/02/2004 SSANDARA 00000025 09925659

02 FC:1806

180.00 OP

Substitute for form 1449A/PTO & 1449B/PTO  <b>THIRD</b> <b>INFORMATION DISCLOSURE</b> <b>STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)			<b>Complete if Known</b>	
Sheet <b>1</b> of <b>2</b>			Application Number	09/925,659
			Filing Date	August 10, 2001
			First Named Inventor	Einar STEFANSSON
			Examiner Name	Zohreh A. Fay
			Attorney Docket Number	032904-001



### U.S. PATENT DOCUMENTS

Examiner Initials	Document Number	Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Issue/Publication Date (MM-DD-YYYY)
	6,156,785		Stefansson et al.	12-05-2000

RECEIVED

MAR 09 2004

### FOREIGN PATENT DOCUMENTS

Examiner Initials	Document Number	Kind Code (if known)	Country	Date of Publication (MM-DD-YYYY)	Translation	
					Yes	No
	99/37292	A2 & A3	WO	07-29-1999		

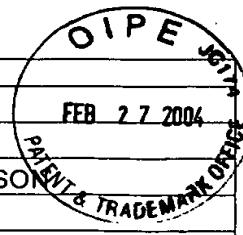
### NON-PATENT LITERATURE DOCUMENTS

Examiner Initials	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.
	Kristinsson, J.K., <i>Diabetic retinopathy. Screening and prevention of blindness. A doctoral thesis.</i> Acta Ophthalmologica Scandinavica Supplement., 1997(223): pp. 1-76, published by Scriptor, Copenhagen, Denmark. [1]
	Kristinsson, J.K., et al., <i>Screening for eye disease in type 2 diabetes mellitus.</i> Acta Ophthalmol (Copenhagen), 1994. 72(3): pp. 341-6, published by Scriptor, Copenhagen, Denmark. [2]
	Kristinsson, J.K., et al., <i>Systematic screening for diabetic eye disease in insulin dependent diabetes.</i> Acta Ophthalmol (Copenhagen), 1994. 72(1): pp. 72-8, published by Scriptor, Copenhagen, Denmark. [3]
	Klein, R., et al., <i>The Wisconsin epidemiologic study of diabetic retinopathy. XI The incidence of macular edema.</i> Ophthalmology, 1989. 96(10): pp. 1501-10, published by American Academy of Ophthalmology, Philadelphia, PA. [4]
	Klein, R., et al., <i>The Wisconsin epidemiologic study of diabetic retinopathy. III Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years.</i> Arch Ophthalmol, 1984. 102(4): pp. 527-32, published by American Medical Association, Chicago, IL. [5]
	Klein, R., et al., <i>The Beaver Dam Eye Study. Retinopathy in adults with newly discovered and previously diagnosed diabetes mellitus.</i> Ophthalmology, 1992. 99(1): pp. 58-62, published by American Academy of Ophthalmology, Philadelphia, PA. [6]
	Kalm, H., R. Egertsen, and G. Blohme, <i>Non-stereo fundus photography as a screening procedure for diabetic retinopathy among patients with type II diabetes. Compared with 60D enhanced slit-lamp examination.</i> Acta Ophthalmol (Copenhagen), 1989. 67(5): pp. 546-53, published by Scriptor, Copenhagen, Denmark. [7]
	Nielsen, N.y., <i>The prevalence and causes of impaired vision in diabetics. An epidemiological study of diabetes mellitus on the island of Falster, Denmark.</i> Acta Ophthalmologica., 1982. 60(5): pp. 677-91, published by Scriptor, Copenhagen, Denmark. [8]
	Chen, M.S., et al., <i>Prevalence and risk factors of diabetic retinopathy among noninsulin-dependent diabetic subjects.</i> Am J Ophthalmol, 1992. 114(6): pp. 723-30, published by Ophthalmic Pub. Co., Chicago, IL. [9]
	Sparrow, J.M., et al., <i>The prevalence of diabetic retinopathy and maculopathy and their risk factors in the non-insulin-treated diabetic patients of an English town.</i> Eye, 1993. 7 ( Pt 1): pp. 158-63, published by Ophthalmological Society of the United Kingdom, London, England. [10]

Examiner Signature	Date Considered	
--------------------	-----------------	--

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

Substitute for form 1449A/PTO & 1449B/PTO		Complete if Known	
<b>THIRD INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)		Application Number	09/925,659
		Filing Date	August 10, 2001
		First Named Inventor	Einar STEFANSSON
		Examiner Name	Zohreh A. Fay
		Attorney Docket Number	032904-00
Sheet	2	of	2



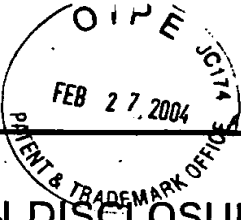
**RECEIVED**  
MAR 09 2004

### NON-PATENT LITERATURE DOCUMENTS

Examiner Initials	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.
	CLINICAL OPHTHALMOLOGY, ed. Thomas David Duane, CD Rom 2002 edition, chapter by J. Arch McNamara and William Tasman on retinopathy of prematurity, published by Medical Dept. Harper & Row, Hagerstown, MD. [11]
	CLINICAL OPHTHALMOLOGY, A SYSTEMIC APPROACH, 2 <sup>nd</sup> edition, ed. Jack J. Kanski, 1989, pp. 330-334, published by Butterworths, London, England. [12]
	CLINICAL OPHTHALMOLOGY, ed. Thomas David Duane, CD Rom 2002 edition, chapter by Donald A. Gagliano, Lee M. Jampol and Maurice F. Rabb on sickle cell disease, published by Medical Dept. Harper & Row, Hagerstown, MD. [13]
	CLINICAL OPHTHALMOLOGY, ed. Thomas David Duane, CD Rom 2002 edition, chapter by George F. Sanborn, Larry E. Magargal and Edward A. Jaeger on venous occlusive disease of the retina, published by Medical Dept., Harper & Row, Hagerstown, MD. [14]
	Frank, Robert N., <i>Diabetic Retinopathy</i> , New England Journal of Medicine 350:48-58, January 1, 2004, published by Massachusetts Medical Society, Boston, MA.
	Aiello, Lloyd M., M.D., <i>Prospectives on Diabetic Retinopathy</i> , American Journal of Ophthalmology, Vol. 136, Issue 1, 122-135, July 2003, published by Elsevier Science Inc., New York, New York.
	Fong, Donald S., MD, MPH, <i>Changing Times for the Management of Diabetic Retinopathy</i> , Survey of Ophthalmology, Vol. 47, Supp. 2, S238-S245, December 2002, published by Elsevier Science, Inc., New York, New York.
	Fong, Donald S., MD, MPH et al., <i>Diabetic Retinopathy</i> , Diabetes Care 26:S99-S102, 2003, published by the American Diabetes Association, Alexandria, VA.

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.



Substitute for form 1449A/PTO

INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT

ATTORNEY'S DKT NO.

032904-001

APPLICATION NO.

09/925,659

APPLICANT

Einar STEFÁNSSON

FILING DATE

August 10, 2001

GROUP

1614

## U.S. PATENT DOCUMENTS

Examiner Initials	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication (MM-DD-YYYY)
	Number	Kind Code (if known)		
	4,677,115		Baldwin et al	06/30/1987
	4,797,413		Baldwin et al	01/10/1989

RECEIVED  
MAR 08 2004

## FOREIGN PATENT DOCUMENTS

Examiner Initials	Foreign Patent Document		Country	Date of Publication (MM-DD-YYYY)	Translation	
	Number	Kind Code (if known)			Yes	no

## NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Include name of author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.		
	Stefánsson, <i>Graefe's Archiv. Clin. Exp. Ophthalmol.</i> , Vol. 228, pp. 120-123 (1990), published by Springer-Verlag, Berlin.		
	Novack et al, <i>Exp. Eye. Res.</i> , Vol. 50, pp. 289-296 (1990), published by Academic Press, London.		
	Stefánsson et al, <i>Trans. Am. Ophthal. Soc.</i> , Vol. 79, pp. 307-334 (1981), published for the American Ophthalmological Society by the Whiting Press, Rochester, Minn.		
	Stefánsson et al, <i>Am. J. Ophthalmology</i> , Vol. 101, pp. 657-664 (1986), published by Ophthalmic Pub. Co., Chicago.		
	Stefánsson et al, <i>Am. J. Ophthalmology</i> , Vol. 113, pp. 36-38 (1992), published by Ophthalmic Pub. Co., Chicago.		
Examiner Signature		Date Considered	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. SEND TO: Assistant Commissioner for Patents, Washington, D.C. 20231.